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ORIGINAL RESEARCH

Ticagrelor is Not Superior to Clopidogrel in Patients With Acute Coronary Syndromes Undergoing PCI: A Report from Swedish Coronary Angiography and Angioplasty Registry

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BACKGROUND: Ticagrelor reduces ischaemic end points in acute coronary syndromes. However, outcomes of ticagrelor versus clopidogrel in real-world patients with acute coronary syndromes treated with percutaneous coronary intervention (PCI) remain unclear. We sought to examine whether treatment with ticagrelor is superior to clopidogrel in unselected patients with acute coronary syndromes treated with PCI.

METHODS AND RESULTS: We used data from SCAAR (Swedish Coronary Angiography and Angioplasty Registry) for PCI performed in Västra Götaland County, Sweden. The database contains information about all PCI performed at 5 hospitals (~20% of all data in SCAAR). All procedures between January 2005 and January 2015 for unstable angina/non–ST-segment–elevation myocardial infarction and ST-segment–elevation myocardial infarction were included. We used instrumental variable 2-stage least squares regression to adjust for confounders. The primary combined end point was mortality or stent thrombosis at 30 days, secondary end points were mortality at 30 days and 1-year, stent thrombosis at 30 days, in-hospital bleeding, in-hospital neurologic complications and long-term mortality. A total of 15 097 patients were included in the study of which 2929 (19.4%) were treated with ticagrelor. Treatment with ticagrelor was not associated with a lower risk for the primary end point (adjusted odds ratio [aOR], 1.20; 95% CI, 0.87–1.61; *P*=0.250). Estimated risk of death at 30 days (aOR, 1.18; 95% CI, 0.88–1.64; *P*=0.287) and at 1-year (aOR, 1.28; 95% CI, 0.86–1.64; *P*=0.556) was not different between the groups. The risk of in-hospital bleeding was higher with ticagrelor (aOR, 2.88; 95% CI, 1.53–5.44; *P*=0.001).

CONCLUSIONS: In this observational study, treatment with ticagrelor was not superior to clopidogrel in patients with acute coronary syndromes treated with PCI.

Key Words: acute coronary syndrome ■ clopidogrel ■ non-ST–segment-elevation myocardial infarction ■ ST-segment–elevation myocardial infarction ■ $P2Y_{12}$ receptor antagonists ■ percutaneous coronary intervention ■ ticagrelor ■ unstable angina

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CLINICAL PERSPECTIVE

What Is New?

- Different from the results from PLATO (Study of Platelet Inhibition and Patient Outcomes), ticagrelor was not superior to clopidogrel in this observational all-comer analysis of patients with acute coronary syndromes undergoing percutaneous coronary intervention in Western Sweden.
- In the present analysis treatment with ticagrelor was not associated with any mortality benefits in comparison with clopidogrel while the incidence of in-hospital bleeding was significantly increased.

What Are the Clinical Implications?

- Benefits of ticagrelor, as demonstrated in the PLATO trial, may not be externally valid when applied to unselected patients with acute coronary syndromes undergoing percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

HR	hazard ratio
PCI	percutaneous coronary intervention
PLATO	Study of Platelet Inhibition and Patient Outcomes
SCAAR	Swedish Coronary Angiography and Angioplasty Registry
STEMI	ST-segment–elevation myocardial infarction
SWEDEHEART	The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies

Current European and American guidelines commend ticagrelor over clopidogrel for treatment of patients with acute coronary syndrome (ACS).[1,2] These guidelines are based on the PLATO (Study of Platelet Inhibition and Patient Outcomes) trial which demonstrated that ticagrelor improved the composite end point of vascular death, non-fatal myocardial infarction, or stroke.[3] In addition, it has been argued that ticagrelor also decreases all-cause mortality in ACS. Since then, ticagrelor has been increasingly endorsed as the favored $P2Y_{12}$ receptor antagonist worldwide.[1,2,4] However, since the publication of the PLATO trial 1 decade ago, observational studies in unselected populations with ACS treated with ticagrelor have generated conflicting results. While some post-marketing observational reports confirmed the PLATO data,[5–7] other studies reported that ticagrelor is not superior to clopidogrel.[8–11] This discrepancy has revived the discussion about the external validity of the PLATO trial and constitute the rationale for our analysis. Thus, we sought to investigate whether treatment with ticagrelor is superior to clopidogrel in an unselected population of patients with ACS who were treated with PCI.

METHODS

Database and Study Population

We used data from SCAAR (Swedish Coronary Angiography and Angioplasty Registry) database reported from 5 hospitals within the Västra Götaland County in western Sweden—representing ≈20% of the total SCAAR registry. Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the SCAAR working group via the corresponding author of this paper. All PCI procedures between 2005 and 2015 for unstable angina/non–ST-segment–elevation myocardial infarction and ST-segment–elevation myocardial infarction (STEMI) were included. Unstable angina/non–ST-segment–elevation myocardial infarction and STEMI were defined according to the diagnostic criteria established by the European Society of Cardiology.[1] SCAAR is a web-based platform (established in 1992), containing >250 clinical, angiographic, and PCI-related variables which document the entire interventional process (www.ucr.uu.se/swedeheart). Swedish Health Authorities sponsor the registry with no funding from commercial interest. SCAAR is an integral part of the larger SWEDEHEART (The Swedish Web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies) registry platform. More detailed information about SWEDEHEART has been published elsewhere.[12,13] The SCAAR database merged with the national death registry—managed by the Swedish National Board of Health and Welfare—to obtain information about the vital status. The ethical committee at the University of Gothenburg has approved the study protocol. Informed consent was not required. Additional methods can be found in Data S1.

Statistical Analysis

Continuous variables are shown as mean±SD and categorical variables are presented as frequencies. Normal distribution was assessed by the Shapiro-Wilk

test as well as inspection of histograms. Linear regression was used to test the intergroup differences in continuous variables while logistic regression was used for categorical variables.

Missing data were imputed with the multiple imputation chain-equation method[14,15] with 5 data sets. The calendar year, an indicator of missingness and an event indicator were included as regular variables.[16] Continuous variables were imputed by ordinary least-squares multiple regression, binary variables by logistic regression, and categorical variables by multinomial logistic regression. The imputation procedure and subsequent analyses were done according to Rubin's protocol[17] under the assumption that missing data are missing at random.

We based our primary statistical model on the instrumental variable analysis to reduce bias because of unmeasured and unknown confounders. This method is a post-hoc analytic technique based on statistical principles similar to those used in the analysis of randomized controlled trials[18–20] (see supplement for more information). In addition to the instrumental variable, propensity score (as continuous variable) was entered into 2-stage least squares regression. The score was calculated from the logistic model based on all variables presented in Tables 1 and 2 that were significantly different ($P<0.05$) between the 2 groups. We used multilevel Cox proportional-hazards regression using the same instrumental variable estimator and propensity score as in the primary model based on 2-stage least squares regressions to compare the groups long-term mortality. Because the SCAAR registry is a hierarchical database with clustering of patients within hospitals and regions, we entered individual hospitals into the regression model as random effects variables. We assessed trends in 30-days and 1-year mortality over the study period by including the calendar year into the logistic regression as a continuous variable in addition to age and sex.

For sensitivity analysis we used propensity score models based on the inverse probability of treatment weighting.[22] Significant predictors of treatment with ticagrelor for each patient were identified by fitting a logistic regression model with (1) a binary dependent variable representing treatment ticagrelor or clopidogrel and (2) candidate variables consisting of the patient-related predictors of the type of therapy used. All variables in Tables 1 and 2 and hospital, were entered into the logistic model.

Post-Estimation Diagnostics

Goodness-of-fit (calibration) for the models was assessed with the Hosmer–Lemeshow test. Multicollinearity between the variables in the model was assessed by calculation of the variance inflation factor. All statistical analyses were performed using Stata software (version 16.0, StataCorp, College Station, Texas, USA). Instrumental variable 2-stage least squares regression models were completed using the IVREG2 module.[23] All tests were 2-tailed, and a $P<0.05$ was considered statistically significant. Because of multiple analyses, $P<0.05$ was expected to occur by chance in 1 out of 20 analyses. The validity of instrumental variables was examined by calculation of the standardized difference of variables that reflects known patient's characteristics and procedural details in treated and untreated patients stratified on the calendar year during the study period. We used logistic regression to evaluate the predictive power of instruments for treatment with $P2Y_{12}$ antagonists as well as for primary and secondary outcomes. All tests were 2-tailed, and $P<0.05$ was considered statistically significant. All statistical analyses were performed using Stata software (version 16.0, StataCorp, College Station, Texas, USA). All tests were 2-tailed and a $P<0.05$ was considered statistically significant.

RESULTS

Baseline Characteristics and Treatments

A total of 15 097 patients were included in the study of which 12 168 (80.6%) were treated with clopidogrel and 2929 (19.4%) were treated with ticagrelor. Baseline patients' characteristics are presented in Table 1 and procedure-related details are presented in Table 2. Women represented 27% of all patients and STEMI was reported in 44%; 30% of all patients were >75 and 16% had diabetes mellitus. We found no difference between the 2 groups on age, sex, creatine clearance, body mass index, diabetes mellitus, smoking habits, treated vessel, culprit vessels occlusion, and the use of thrombus aspiration during PCI. Patients treated with a ticagrelor were more likely to have had previous myocardial infarction, prior PCI, and prior coronary artery by-pass surgery. Patients treated with clopidogrel were more likely to have hyperlipidemia, non-ST segment elevation (NSTE)-ACS, cardiogenic shock, and to be treated with intra-aortic balloon pump but were less likely to have a radial access and to be treated with PCI during off-hours. Patients treated with ticagrelor were more often treated with bivalirudin but less often with GP2b/3a receptor antagonist. They were more likely to be completely revascularized and to have thrombus aspiration before stent placement but were less likely to receive direct stenting. Drug-eluting stents, fractional flow reserve/instantaneous wave–free ratio, intravascular ultrasound and optical coherence tomography were more often used in patients treated with ticagrelor; 4515 (30%) patients were treated with PCI after the change from clopidogrel to ticagrelor as the default

Table 1. Patients' Characteristics at Baseline

	Clopidogrel (n=12 168)	Ticagrelor (n=2929)	*P* Value
Age, y			0.829
Mean (SD)	67.30 (11.48)	67.25 (11.64)	
Median (Q1, Q3)	68.0 (59.0, 76.0)	67.0 (59.0, 76.0)	
Age >75 y — no. (%)			0.593
Yes	3613 (29.7)	855 (29.2)	
Creatine clearance			0.964
Mean (SD)	86.85 (34.9)	86.81 (35.7)	
Median (Q1, Q3)	82.8 (62.7, 106.9)	83.7 (60.9, 106.8)	
BMI			<0.001
Mean (SD)	27.1 (5.2)	27.6 (8.70)	
Median (Q1, Q3)	26.5 (24.2, 29.3)	26.7 (24.3, 29.7)	
Sex — no. (%)			0.771
Male	8812 (72.4)	2129 (72.7)	
Female	3356 (27.6)	800 (27.3)	
Diabetes mellitus — no. (%)			0.192
Yes	1865 (15.3)	481 (16.4)	
Missing	140 (1.2)	11 (0.4)	
Hypertension — no. (%)			0.007
Yes	5606 (46.1)	1446 (49.4)	
Missing	363 (3.0)	54 (1.8)	
Hyperlipidaemia — no. (%)			<0.001
Yes	4840 (41.2)	964 (33.7)	
Missing	418 (3.4)	69 (2.6)	
Smoking — no. (%)			0.058
Never smoker	4644 (38.2)	1151 (39.3)	
Previous smoker	3541 (29.1)	853 (29.1)	
Active smoker	2637 (21.7)	723 (27.3)	
Missing	1346 (11.1)	202 (6.9)	
Previous myocardial infarction — no. (%)			0.002
Yes	2275 (18.7)	466 (15.9)	
Missing	180 (1.5)	46 (1.6)	
Previous CABG — no. (%)			0.010
Yes	858 (7.1)	163 (5.6)	
Missing	4 (0.0)	0 (0.0)	
Previous PCI — no. (%)			0.030
Yes	1572 (12.9)	335 (11.4)	
Indication for PCI — no. (%)			<0.001
UA/NSTEMI	6947 (57.1)	1491 (50.9)	
STEMI	5221 (42.9)	1438 (49.1)	
Cardiogenic shock — no. (%)			0.032
Yes	250 (2.9)	64 (2.2)	
Missing	3637 (29.9)	2 (0.1)	
Procedure performed off-hours/regular hours — no. (%)			<0.001
Acute-regular hours	3094 (25.7)	746 (25.5)	
Acute-off-hours	3924 (32.6)	1078 (36.9)	
Subacute-regular hours	4628 (38.0)	800 (27.3)	
Subacute-off-hours	388 (3.2)	298 (10.2)	
Missing	134 (1.1)	7 (0.2)	

BMI indicates body mass index; CABG, coronary artery by-pass surgery; NSTEMI, non–ST-segment-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

Table 2. Angiography and PCI

	Clopidogrel (n=12 168)	Ticagrelor (n=2929)	*P* Value
Number of stents			<0.001
Mean (SD)	1.71 (0.98)	1.88 (1.15)	
Median (Q1, Q3)	1.0 (1.0, 2.0)	2.0 (1.0, 2.0)	
Total stent length, mm			<0.001
Mean (SD)	30.83 (19.80)	39.36 (27.97)	
Median (Q1, Q3)	24.0 (18.0, 39.0)	30.0 (18.0, 50.0)	
Mean stent diameter, mm			<0.001
Mean (SD)	3.08 (0.49)	3.01 (0.45)	
Median (Q1, Q3)	3.0 (2.8, 3.5)	3.0 (2.8, 3.3)	
Total contrast, mL			<0.001
Mean (SD)	193.10 (88.44)	177.83 (83.45)	
Median (Q1, Q3)	173.0 (130.0, 234.0)	160.0 (120.0, 219.0)	
Arterial access — no. (%)			<0.001
Femoral	6572 (54.3)	598 (20.8)	
Radial	5224 (43.2)	2158 (75.0)	
Other	303 (2.5)	120 (4.2)	
Severity of coronary disease — no (%)			0.036
Normal	44 (0.4)	3 (0.1)	
Single vessel	5935 (48.8)	1470 (50.2)	
Multi-vessel	6189 (50.9)	1456 (49.7)	
Treated vessel — no. (%)			0.166
RCA	3791 (31.2)	916 (31.3)	
LAD	5415 (44.5)	1288 (44.0)	
LCx	2792 (22.9)	668 (22.8)	
LM	169 (1.4)	57 (1.9)	
Type of lesion — no. (%)			0.002
De novo	11787 (96.9)	2874 (98.1)	
Other restenosis	38 (0.3)	6 (0.2)	
In-stent restenosis	334 (2.7)	49 (1.7)	
Lesion classification — no. (%)			<0.001
A	1186 (9.8)	282 (9.6)	
B1	3808 (31.3)	957 (32.7)	
B2	4085 (33.6)	837 (28.6)	
C	2430 (20.0)	571 (19.5)	
B1 Bifurcation	218 (1.8)	122 (4.2)	
B2 Bifurcation	277 (2.3)	113 (3.9)	
C Bifurcation	139 (1.1)	42 (1.4)	
Other	15 (0.1)	5 (0.2)	
Culprit lesion occlusion — no. (%)			0.367
No	8276 (68.0)	1951 (66.7)	
Yes <3 mo	3736 (30.7)	938 (32.0)	
Yes >3 mo[21]	156 (1.3)	40 (1.3)	
Methods used — no. (%)			<0.001
POBA	405 (3.3)	66 (2.3)	
Direct stent	3944 (32.4)	832 (28.4)	
POBA and stent	7661 (63.0)	1972 (67.3)	
Atherectomy	14 (0.1)	1 (0.0)	
Rotablator	9 (0.1)	2 (0.1)	

(*Continued*)

Table 2. Continued

	Clopidogrel (n=12 168)	Ticagrelor (n=2929)	*P* Value
Wire-attempt	53 (0.4)	12 (0.4)	
DEB	14 (0.1)	7 (0.2)	
DEB and stent	6 (0.0)	1 (0.0)	
Other	61 (0.5)	36 (1.3)	
Type of stent — no. (%)			<0.001
BMS	9324 (76.6)	309 (10.5)	
DES	2844 (23.4)	2620 (89.5)	
Thrombus aspiration — no. (%)			0.090
Yes	1054 (8.7)	283 (9.7)	
Missing	11 (0.1)	0	
FFR/iFR — no (%)			<0.001
Yes	224 (1.8)	150 (5.1)	
Missing	2 (0.0)	1 (0.0)	
IVUS — no. (%)			0.060
Yes	428 (3.5)	129 (4.4)	
Missing	2 (0.0)	1 (0.0)	
OCT — no. (%)			<0.001
Yes	5 (0.0)	27 (0.9)	
Missing	1 (0.0)	1 (0.0)	
Complete revascularisation — no. (%)			<0.001
Yes	7263 (59.7)	1882 (64.3)	
Missing	8 (0.1)	7 (0.2)	
Intra-aortic balloon pump — no. (%)			<0.001
Yes	360 (2.9)	20 (0.7)	
Missing	12 (0.1)	0 (0)	
UH/LMWH — no. (%)			<0.001
Yes	6225 (51.2)	2378 (81.2)	
Missing	2 (0.0)	0 (0.0)	
Bivalirudin — no. (%)			<0.001
Yes	7500 (63.7)	1511 (51.6)	
Missing	1 (0.0)	0 (0.0)	
GP2b/3a inhibitor — no. (%)			<0.001
Yes	3366 (27.7)	119 (4.1)	

BMS indicates bare metal stent; CTO, chronic total occlusion; DEB, drug-eluting balloon; DES, drug-eluting stent; FFR, fractional flow reserve; GP2b/3a, glycoprotein 2b/3a receptor-inhibitor; iFR, instantaneous wave–free ratio; IVUS, intravascular ultrasound; LAD, left anterior descending coronary artery; LCx, left circumflex artery; LM, left main; LWMH, low molecular weight heparin; OCT, optical coherence tomography; POBA, plain old balloon angioplasty; RCA, right coronary artery; and UH, unfractionated heparin.

$P2Y_{12}$ receptor antagonist in February 2012 (Figure 1). Of these, 1587 (35%) were treated with clopidogrel.

Clinical Outcome

Primary End Point

The primary outcome was assessed at 30 days after the index hospitalization. Information about vital status and stent thrombosis was available for all included patients. There were 555 events at 30 days of which 53 (9.5%) were stent thromboses. Treatment with ticagrelor was not associated with a lower risk for the primary end point (adjusted odds ratio [aOR], 1.20; 95% CI, 0.87–1.61; *P*=0.250, Table 3).

Secondary End Points

Between 2000 and 2015, the overall mortality at 30 days (aOR, 1.01; 95% CI, 0.97–1.06, Ptrend=0.514), (Figure 2) and at 1-year (aOR, 1.02; 95% CI, 0.99–1.06, Ptrend=0.174), (Figure 3) did not change. A total of 844 (5.6%) were dead at 1-year after the index hospitalization. Estimated risk of death at 30 days (aOR, 1.18; 95% CI, 0.88–1.64; *P*=0.287) and 1-year (aOR, 1.28; 95% CI, 0.86–1.93; *P*=0.222) was not different between the

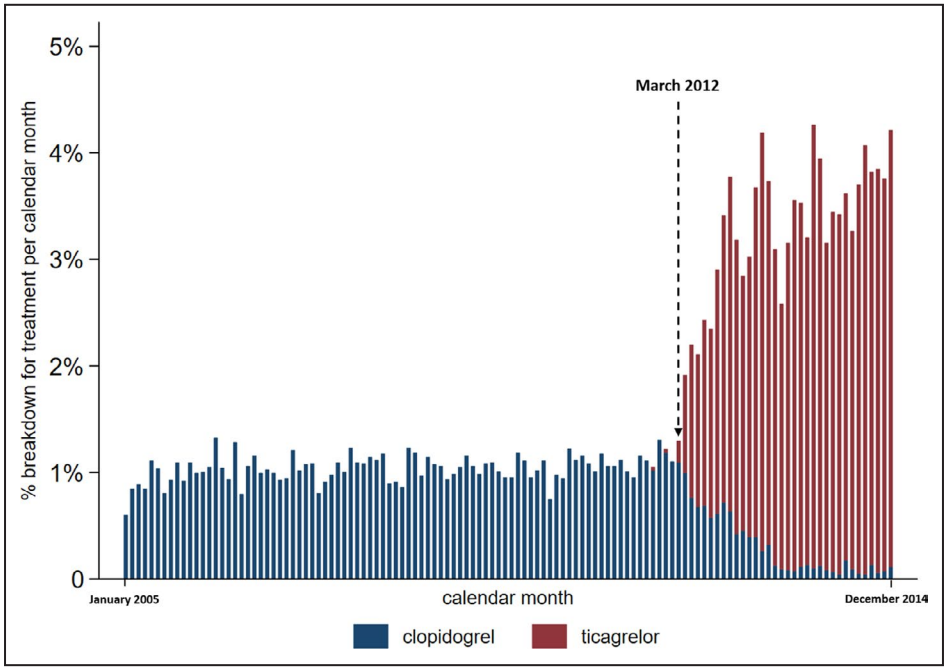

Figure 1. Percentage breakdown per calendar month for use of the 2 $P2Y_{12}$ antagonists—clopidogrel and ticagrelor—over the study period between January 2005 and January 2015 in Västra Götaland County.

In February 2012, the regional executive board decided to replace clopidogrel with ticagrelor as the default $P2Y_{12}$ receptor antagonist for patients with ACS. Figure 1 depicts the percentage breakdown for all patients treated during the study period with either clopidogrel (n=12 168; blue) or ticagrelor (n=2929; red) per calendar month during the study period. Percentages for each column per month thus add up to the entire study population (100%) for each treatment group.

2 groups (Table 3). There was no difference in definite stent thrombosis at 30 days (aOR, 1.30; 95% CI, 0.54–3.10; *P*=0.556), (Table 3)]. Data about in-hospital bleeding and in-hospital neurologic complications were missing in 1757 (11.6%) patients. The risk of in-hospital bleeding was higher with ticagrelor (aOR, 2.88; 95% CI, 1.53–5.44; *P*=0.001), Table 3). There was no difference in neurologic complications during hospitalization (aOR, 0.95; 95% CI, 0.44–2.02; *P*=0.891), The mean follow-up time was 1633±1048 (range 0–3692) in the whole cohort. Patients treated with clopidogrel had longer mean follow-up time (1918±963, range 0–3692) than patients treated with ticagrelor (454±280, range 0–1179). There were 2618 (17.3%) deaths during the total follow-up time. We found no significant difference in long-term mortality between the 2 groups (adjusted hazard ratio [aHR], 1.07; 95% CI, 0.89–1.29; P=0.437), (Figure 4). We found no significant difference in long-term major adverse cardiovascular events (death, myocardial infarction, or stroke) between the 2 groups (aHR, 1.08; 95% CI, 0.91–1.28; *P*=0.400). We found no interaction between the $P2Y_{12}$ antagonist and age, sex, diabetes mellitus, STEMI/non–ST-segment–elevation myocardial infarction, the use of GP2b/3a inhibitor and access site for any of primary or secondary end points (all $P_{interaction}$>0.05).

Sensitivity Analyses

The results from the sensitivity analyses based on logistic regression adjusted with inverse probability of treatment weighted propensity score are presented in Table S1. Generally, the results were in agreement with the primary model with the estimated risk of in-hospital bleeding (with ticagrelor) being higher than in the primary model.

Data Analysis and Post-Estimation Diagnostics

Post-estimation analysis for the logistic regression models by Hosmer–Lemeshow test showed adequate goodness-of-fit for the models (*P*>0.05). Squared covariate terms had no explanatory power in any of the models (link test, *P*>0.05). The average variance inflation factor was <5.0 for all models, indicating a lack of multicollinearity between the variables.

DISCUSSION

Among 15 097 patients with ACS undergoing PCI between January 2005 and January 2015 in Sweden, treatment with ticagrelor was not associated with a lower risk of all-cause mortality and stent thrombosis. However,

Table 3. Clinical Outcomes

Clinical Outcome	Clopidogrel (n=12 168)	Ticagrelor (n=2929)	Adjusted Odds Ratio	95% CI	*P* Value	Missing n (%)
Primary end point						
Death or definite stent thrombosis at 30 d — n (%)	439 (3.6)	116 (4.0)	1.20	0.87–1.61	0.250	0
Secondary end points						
Death, myocardial infarction, or stroke at 30 d — n (%)	697 (6.5)	205 (8.1)	1.25	0.95–1.63	0.104	2128 (14.1)‡
Death, myocardial infarction, or stroke at 1 y — n (%)	1441 (13.4)	340 (13.4)	1.15	0.93–1.45	0.192	2128 (14.1)‡
Death at 30 d — n (%)	439 (3.6)	116 (4.0)	1.18	0.88–1.64	0.287	0
Definite stent thrombosis at 30 d — n (%)	45 (0.4)	8 (0.3)	1.30	0.54–3.10	0.556	0
Death at 1 y — no. (%)	729 (6.1)	115 (6.3)	1.28	0.86–1.93	0.222	0
Definite stent thrombosis at 1 y — no. (%)	76 (0.7)	10 (0.4)	1.18	0.54–2.56	0.682	0
In-hospital bleeding — no. (%)*	489 (4.2)	163 (6.6)	2.88	1.53–5.44	0.001	979 (6.5)
Neurologic complication — no. (%)†	19 (0.2)	5 (0.2)	0.95	0.44–2.02	0.891	778 (5.2)

*Major bleeding (Bleeding Academic Research Consortium type 3), minor bleeding (Bleeding Academic Research Consortium type 2).
†Stroke or transient ischemic attack.
‡Data missing for myocardial infarction and stroke.

ticagrelor-treated patients had a higher risk of in-hospital bleeding. These findings are different from the PLATO trial and raise important matters for discussion.

Our results are supported by several observational studies. In a study performed within the British Cardiovascular Intervention Society PCI registry, the authors investigated the impact of $P2Y_{12}$ receptor antagonists on all-cause mortality at 1 year in patients with STEMI treated with primary PCI.[9] In agreement with our findings, this study showed no difference in mortality between ticagrelor and clopidogrel. However, the authors reported improved outcome in patients treated with prasugrel compared both with clopidogrel and ticagrelor. Moreover, in a population of Dutch patients with ACS (contemporaneous with our population), treatment with ticagrelor increased risk of the composite net clinical end point of all-cause death, myocardial infarction, stroke, or major bleeding at 1 year.[8] While ticagrelor was not associated with benefits on ischemic end points, the risk of major bleeding was almost 3 times higher in the patients treated with ticagrelor. Finally, a recently published

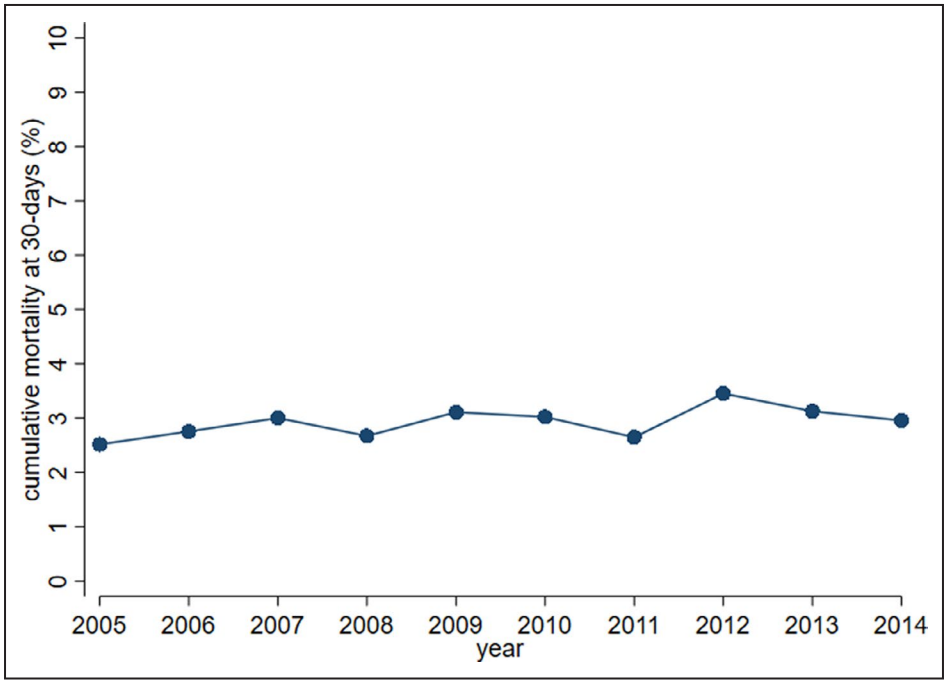

Figure 2. Cumulative incidence of mortality at 30-days in Västra Götaland County between 2005 and 2015.

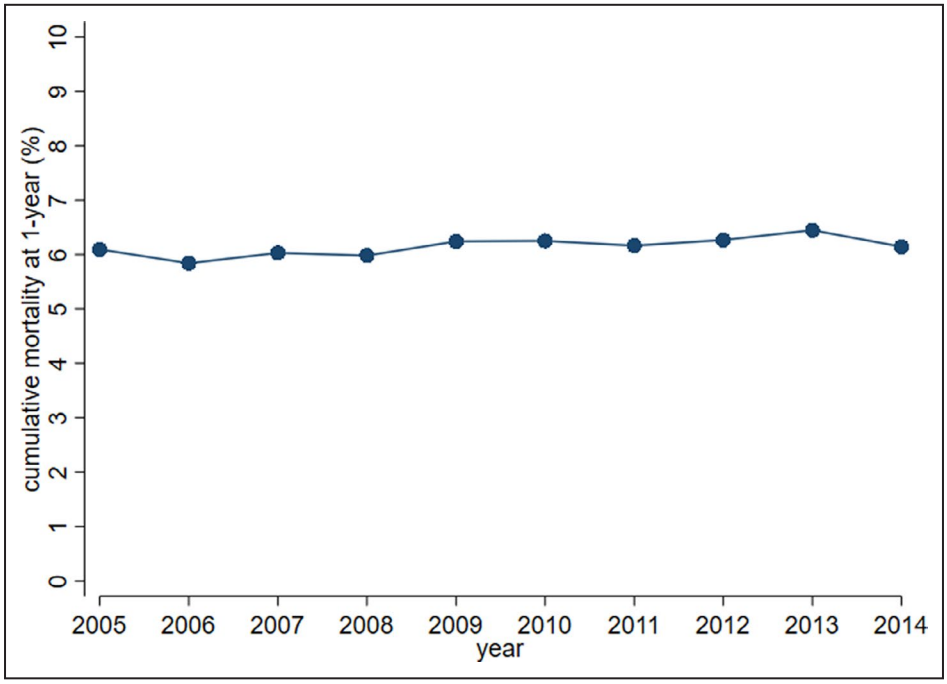

Figure 3. Cumulative incidence of mortality at 1 year in Västra Götaland County between 2005 and 2015.

Canadian registry analysis of comparable size and patient case–mix as in our study, did not show that ticagrelor was superior to clopidogrel regarding major adverse cardiovascular events in patients with ACS undergoing PCI.[11]

One previous observational study from SWEDEHEART reported that ticagrelor was associated with lower all-cause mortality but with higher risk of bleeding.[5] However, while the previous study evaluated only survival after hospital discharge (1434 cases

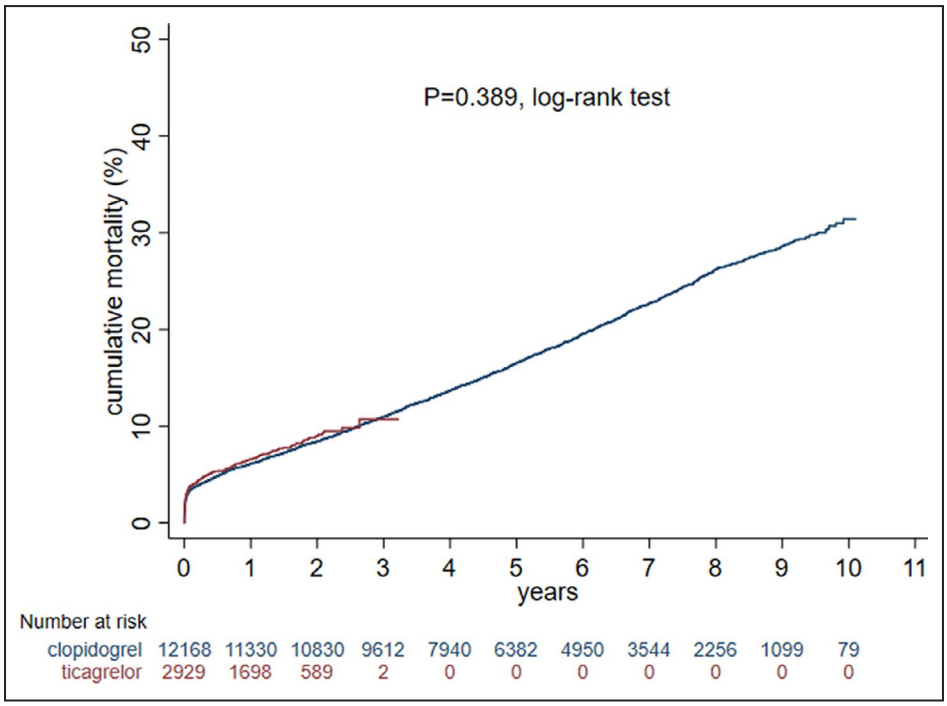

Figure 4. Long-term mortality in patients treated with ticagrelor and clopidogrel in Västra Götaland County between 2005 and 2015.

of in-hospital deaths were excluded from the analysis), the present study includes all deaths from hospital admission until the end of the follow-up time. We argue that our approach is more appropriate for the assessment of the external validity of the PLATO trial for all-cause mortality.

Our results are also supported by the evidence from several randomized controlled trials. First, the cluster-randomized ARTEMIS (Affordability and Real-World Antiplatelet Treatment Effectiveness After Myocardial Infarction Study) investigators assessed the impact of medication co-payment vouchers on the $P2Y_{12}$ receptor antagonists compliance and major adverse cardiovascular events.[24] In >11 000 patients with myocardial infarction from 301 different hospitals in the United States, patients receiving vouchers had higher ticagrelor persistence, but this did not translate into clinical benefit. Also, in the TOPIC trial (Timing of Platelet Inhibition after ACS), de-escalation of $P2Y_{12}$ receptor antagonist (from ticagrelor to clopidogrel) 1 month after PCI was studied in a contemporary ACS population.[25] The risk for the composite net clinical end point (cardiovascular death, unplanned hospitalization, urgent revascularization, stroke, bleeding) at 1-year was lower in patients who switched from ticagrelor to clopidogrel. The difference was driven by an increased incidence of bleeding with no variance in ischemic end points.[8,9]

Why our results differ from the PLATO trial may be explained by the following features. While in PLATO more than one third of patients were treated conservatively, all patients in our study were treated with PCI. Compared with our study, patients in PLATO were younger and more frequently men which confirms well-known discrepancies between randomized clinical trials and unselected patient populations.[26] Consequently, based on the established predictors for bleeding,[27,28] our unselected population may have been more prone to bleeding when exposed to a potent antiplatelet agent. Indeed, the increased risk of bleeding may constitute mediating pathway[29] for the observed absence of mortality benefit with ticagrelor in an unselected population.[8,9] Another simple but potent mediator for attenuation of ticagrelors' efficacy outside randomized clinical trial may be decreased compliance because of the higher rate of adverse events (dyspnea, bleeding), administration of the drug twice per day and higher costs. Indeed, in the PLATO trial, ticagrelor had higher discontinuation rate than clopidogrel with 23% of patients being non-compliant. It seems reasonable to argue that non-compliance with ticagrelor is even higher outside the settings of well-controlled clinical trial and with a different (more non-compliant prone) patient population.

Like many medical novelties after introduction to the market, ticagrelor has imposed a considerable economic burden to healthcare resources. In our region, this additional cost reaches an extra 2.000.000 Euros annually compared with clopidogrel. Yet, the totality of evidence at present time does not unequivocally support the cost-effectiveness of ticagrelor.

Several limitations need to be addressed. Swedish practice and outcomes do not necessarily reflect cardiovascular care in other areas in the world. We acknowledge that observational design of our study produces a risk for residual confounding. However, our statistical models were based on instrumental variable analysis which is one of the best methods to eliminate both known and unknown confounders in observational studies. In addition, most known confounders related to patient's characteristics and procedural details favored ticagrelor. It is plausible that possible unmeasured confounders also favored ticagrelor because these patients were treated during the recent era. The events in the study were not adjudicated by an adjudication committee. However, regular external monitoring and data validation are performed in SWEDEHEART to ascertain high data accuracy.[13] Our data did not allow differentiation between cardiac and non–cardiac death, but mortality is a robust end point. Possibility for administrative errors about citizens' vital status in Sweden is low and nearly 100 percent of deaths are registered within the first month.[30] Finally, we could not account for the duration of antiplatelet treatment and possible cross–over between the groups as this information is not reported to the registry. The analysis was, therefore, based on the intention to treat principle. The recommended duration for dual antiplatelet therapy in patients with ACS has been 12 months during the study period.

In conclusion, in this observational study, treatment with ticagrelor was not superior to clopidogrel in patients with ACS treated with PCI and was associated with an increased risk of bleeding. Benefits of ticagrelor, as demonstrated in the PLATO trial, may not be externally valid when applied to unselected patients with ACS undergoing PCI.

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Supplementary Materials

Data S1
Tables S1
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SUPPLEMENTAL MATERIAL

DATA S1.

SUPPLEMENTAL METHODS

INSTRUMENTAL VARIABLE ANALYSIS

We based our primary statistical model on the instrumental variable analysis to reduce bias due to unmeasured and unknown confounders. This method is a post hoc analytic technique based on statistical principles similar to those used in the analysis of randomized controlled trials[31-33]. To use instrumental variable analysis, one must identify a naturally varying phenomenon in the observed data, which like the act of randomization in an RCT, predicts the treatment that will be assigned to the individual patient. To become a valid instrument, a variable must fulfill some necessary criteria. First, it must be strongly associated with the received treatment. Second, it must not be associated directly or indirectly with the outcome, except through the effect of the treatment itself. The variable with these statistical qualities is called instrumental variable, or instrument. We used the time before and after the switch to ticagrelor as the treatment-preference instruments. Calendar time is frequently employed as instruments because this type of variables usually fulfills the theoretical criteria for a valid instrument[34-36]. Variations in the use of the treatment strategy over time in Sweden is a result of changes in guidelines and reimbursement policies as well as changes in physicians' preference due to the release of new effectiveness and safety information. During the study period in February 2012, the regional executive board responsible for the organization of health care in Västra Götaland County decided to replace clopidogrel with ticagrelor as the default $P2Y_{12}$ receptor antagonist for patients with ACS (Figure 1). We used this swift change in routines as an instrumental variable based on two periods [(before and after February 2012), (Fig. 1)].

Durbin-Wu-Hausman specification test was used to evaluate the presence of residual confounding (endogeneity). The validity of the instrumental variable was tested with the Sargan test. To test for the strength of the instruments, we examined the partial F test from the first-stage regression, which predicts treatment as a function of instrument and covariates. The partial F test has the null hypothesis that the coefficient for the effect of the instrument in the first-stage regression model is zero[37]. An F-statistic greater than 10 indicates that the instrument is not weak. Reported standard errors from IV 2SLS regression are robust and account for clustering of patients within hospitals using the sandwich estimator. Our primary model was based on instrumental variable two-stage least squares (2SLS) regression[33]. The outcome (dependent) variables in the 2SLS regressions were all-cause mortality at 30-days or definite stent thrombosis at 30-days, all-cause mortality 30-days, all-cause mortality at one-year, in-hospital bleeding, in-hospital neurologic complications.

Table S1. Sensitivity analyses with inverse probability of treatment weighted propensity score adjustment.

Clinical outcome	Clopidogrel (N = 12,168)	Ticagrelor (N = 2,929)	Adjusted odds ratio	95% CI	P-value	Missing N (%)
Primary endpoint						
Death or definite stent thrombosis at 30 days — no. (%)	439 (3.6)	116 (4.0)	1.24	0.82-1.89	0.305	0
Secondary endpoints						
Death, myocardial infarction or stroke at 30 days — no. (%)	697 (6.5)	205 (8.1)	1.11	0.81-1.55	0.503	2,128 (14.1) ¤
Death, myocardial infarction or stroke at one year — no. (%)	1,441 (13.4)	340 (13.4)	1.13	0.82-1.57	0.444	2,128 (14.1) ¤
Death at 30 days — no. (%)	400 (3.3)	109 (3.7)	1.19	0.78-1.82	0.403	0
Definite stent thrombosis at 30 days— no. (%)	45 (0.4)	8 (0.3)	1.37	0.28-6.61	0.693	0
Death at one year — no. (%)	729 (6.1)	115 (6.3)	1.03	0.85-2.32	0.184	0
In-hospital bleeding— no. (%)[#]	489 (4.2)	163 (6.6)	3.49	1.67-7.28	0.001	979 (6.5)
Neurologic complication— no. (%)[&]	19 (0.2)	5 (0.2)	1.04	0.24-4.51	0.952	778 (5.2)

[#] major bleeding (BARC type 3), minor bleeding (BARC type 2)
[&] stroke or transient ischemic attack
¤ data missing for myocardial infarction and stroke